# EXHIBIT 28

## REMARKS

Claims 1-7, 9-12, 14-35 and 47 are pending, and are presented for reconsideration. No amendments have been made to the claims.

Applicants gratefully acknowledge the Examiner's withdrawal of the rejection of pending claims over Stamm ('670) and Curtet ('726) .

Claims 1, 4-6, 9-12, 15-21, 23-35 and 47 are newly rejected under 35 U.S.C. §103(a) over U.S. Patent No. 4,800,079 to Boyer (Boyer '079) in view of Kiel EP 0 793 958 (EP 958), or EP 958 in view of Boyer '079. Boyer '079 issued January 24, 1989, and is assigned to Ethypharm, which also owns the instant application.

The Examiner acknowledges that Boyer '079 fails to teach a surfactant in a fenofibrate composition; but relies on EP 958 as teaching a fenofibrate composition comprising fenofibrate, surfactant and polyvinylpyrrolidone and other adjuvants, prepared by mixing, granulating and subsequent drying. The Examiner argues that it would have been obvious for one of ordinary skill in the art to combine Boyer '079 and EP 958.

This rejection is respectfully traversed. The rejection fails to present a *prima facie* case of obviousness for at least the reasons that one of ordinary skill in the art would not have been motivated to combine Boyer '079 and EP 958; and, even if combined, one would not have arrived at the claimed invention; and, even if the two references together suggest the claimed invention, they would not have suggested the surprising and unexpected results achieved.

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art,

to combine the teachings of the references. Second, there must be a reasonable expectation of success. Finally, the prior art references must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure. *In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991).

Boyer '079 discloses the successive layering of an active agent on an inert core with the assistance of a binder. Specifically, an alcohol solution of a water-soluble (hydrophilic) binder is applied to the surface of an inert core. Dry, microcrystalline fenofibrate is then added to the tacky binder layer; and the binder is quickly dried. If the tacky binder layer is not quickly dried, the microscrystalline fenofibrate particles will deform, and lose the dissolution benefits associated with the microcrystalline fenofibrate. The layering of binder and fenofibrate is repeated until the requisite quantity of fenofibrate has been applied to the inert core. Lastly, the granules are coated with a protective layer. (*See* column 2, line 38 to column 3, line 12, of Boyer '079).

The rejection correctly acknowledged that Boyer '079 does not disclose the use of a surfactant, which is required by the present claims. But this is not the only difference. For example, various claims also require a specified weight ratio between fenofibrate and binding cellulose derivative (e.g., claim 21: "... comprising micronized fenofibrate, a surfactant, and a binding cellulose derivative as a solubilization agent, wherein the mass ratio of said fenofibrate to said binding cellulose derivative is between 5/1 and 15/1."). Such relationship is neither taught nor suggested by Boyer '079.

The rejection also mischaracterizes Boyer '079 in other respects. For example, the outer protective layer of Boyer does not form a matrix wherein the fenofibrate is deposited; the outer protective layer is applied over top of the layer of fenofibrate. In fact, it is the water-soluble binder material that serves as a matrix and, ultimately, a dispersant for the fenofibrate. Furthermore, in the example (Col. 3), the amount of fenofibrate is 75.5% rather than 80 %, as asserted.

EP 958 relies upon a process entirely distinct from that of Boyer '079; and produces a distinct product. EP 958 is limited to a fenofibrate formulation fabricated by wet granulation. The wet granulation method produces an irregular mixture lacking the finely layered structure of microscrystalline fenofibrate on an inert core, which is a characteristic of Boyer '079 and the present invention.

In EP 958, fenofibrate particles are mixed together simultaneously with polyvinylpyrrolidone particles, cross-linked polyvinylpyrrolidone particles, and, optionally, other adjuvant particles. There is no rapid drying. The EP 958 mixture is then granulated with an aqueous solution of surfactant(s), and the entire mixture is dried. *See* claim 1 and paragraph 0014, of EP 958.

The resulting product is quite different from the finely layered structure of Boyer 079. Boyer 079 requires a water soluble binder, and an iterative process of finely layered binder and fenofibrate followed by rapid drying (e.g., binder → fenofibrate → rapid drying; binder → fenofibrate ...) to minimize exposure of the microscrystalline fenofibrate to alcohol, which would otherwise destroy the microparticulate structure of fenofibrate. *See*, col. 2, line 64 – col. 3, line 23. Thus, the additives selected for use in the two methods would be expected to be quite different, and to play distinct roles.

In fact, EP 958 expressly distinguishes its process and product from the coated neutral cores of Boyer '079:

> [0021] In contrast to EP-A1-256 933 [the EP equivalent of Boyer '079], according to which an application such as the spraying on of fenofibrate onto the polyvinylpyrrolidone acting solely as a binding agent is carried out, in the process of the invention a mixing of the fenofibrate with the polyvinylpyrrolidone and in addition with cross-linked polyvinylpyrrolidone takes place. There is also the difference from EP-A1-256 933, in which no cross-linked polyvinylpyrrolidone is used, which is even excluded according to its process, because a binding agent that is soluble in water must be used, that in the process of the invention cross-linked polyvinylpyrrolidone particles must be obligatorily also mixed in. A further difference resides in the fact that according to the process of the invention, in contrast to that of the cited publication, the granulation is performed with a surface-active agent in another stage.

EP 958 thus identifies at least four differences between its formulation and Boyer '079:

- Boyer '079 is directed to spray-coated neutral cores while EP 958 is directed to a mixture (i.e., wet granulation);
- Boyer '079 utilizes polyvinylpyrrolidone as the sole binding agent, while EP 958 utilizes both polyvinylpyrrolidone and cross-linked polyvinylpyrrolidone, the latter characterized as being essential ;
- Boyer '079 excludes the use of cross-linked polyvinylpyrrolidone because the binder therein must be hydrophilic, and cross-linked polyvinylpyrrolidone is not hydrophilic; and
- Boyer '079 does not utilize a surfactant, while EP 958 must utilize a surfactant.

Boyer '079 is directed to coated neutral cores, while EP 958 is directed to wet granulation. One of ordinary skill in the art would have recognized that finely layered

microcrystalline fenofibrate coated neutral cores and fenofibrate formulations from wet granulation are as apples and oranges – they are formed by different processes, using different additives that have different properties for different purposes. One of ordinary skill in the art would not have expected that ingredients used in wet granulation would have the same properties and impart the same benefits when used in coating neutral cores, nor would one have expected that products produced by the one are interchangeable with the other. The rejection does not identify any teaching or suggestion to the contrary.

Indeed, EP 958 expressly identifies some of those differences. One of ordinary skill in the art would have understood from EP 958 that materials said to be beneficial – perhaps even necessary - in a wet granulation formulation are not beneficial – and perhaps must be excluded – in a neutral core coated formulation. Thus, there is not only a lack of motivation to combine EP 958 and Boyer '079, but in fact the EP 958 reference itself contains an express teaching away from such a combination.

One of ordinary skill in the art would not have combined Boyer '079 and EP 958 as in the outstanding rejection; and, even if one had so combined those references, there is no showing that one would have arrived at the presently claimed invention, nor would there have been any reasonable expectation of achieving the present unexpected advantages, as described in the Bobotas Declarations. Accordingly, Applicants respectfully submit that the rejection does not present a *prima facie* case of obviousness based on these references. Applicants respectfully request withdrawal of the outstanding rejection of claims 1, 4-6, 9-12, 15-21, 23-35 and 47 under 35 U.S.C. §103(a) based on Boyer '079 and EP 958.

Claims 2, 3, 7, 14 and 22 are newly rejected under 35 U.S.C. §103(a) as being unpatentable over Boyer '079 in view of EP 958, as applied to claims 1, 4-6, 9-12, 15-21 and 23-35 above, and further in view of WO 96/01621. The Examiner acknowledges that neither Boyer '079 nor EP 958 teaches the specific polymer of the rejected claims. WO 621 is relied upon for disclosing the specific polymer.

As noted above, one of ordinary skill in the art would not have been motivated to combine the teachings of Boyer '079 and EP 958; and, even if one had so combined those references, there would not have been any reasonable expectation of success in achieving the benefits and advantages of the presently claimed invention. The addition of WO 621 does not overcome those deficiencies. Therefore, Applicants respectfully submit that the rejection of claims 2, 3, 7, 14 and 22 under 35 U.S.C. §103(a) should also be withdrawn.

Claims 1-7, 9-12, 14-35 and 47 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-45 of copending application Serial No. 10/677,861. Reconsideration of this rejection is respectfully requested for at least the following reasons.

Applicants submit that the claims of the present application and those of the '861 application are drawn to different inventions and are capable of supporting separate patents. Mere overlap in the scope of claims is not, *per se*, double patenting (M.P.E.P. § 804, page 800-19, right hand column).

Moreover, it is the policy of the Patent and Trademark Office to issue an earlier filed application where a provisional obviousness double patenting rejection is the only remaining issue (M.P.E.P. § 804, page 800-17, right hand column).

Claims 1-7, 9-12, 14-35 and 47 allegedly are directed to an invention not patentably distinct from claims 1-45 of commonly assigned application No. 10/677,861 for reasons set forth on page 7 of the Office Action. Respectfully, Applicants disagree and submit that the claims of the respective applications are drawn to patentably distinct inventions.

In view of the foregoing amendments and remarks, applicants respectfully request reconsideration and withdrawal of all outstanding rejections. Applicants submit that the claims are now in condition for allowance, and respectfully request formal notification to that effect. If, however, the Examiner perceives any impediments to such a notice of allowability, whether substantive or formal, the Examiner is encouraged to call Applicants' attorney at the number provided below. Such informal communication will expedite examination and disposition of this case.

Respectfully submitted,

BUCHANAN INGERSOLL PC

Date: April 13, 2006

By: _____
Brian P. O'Shaughnessy
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# EXHIBIT 29

| Notice of Allowability | Application No. 10/030,262 | Applicant(s) CRIERE ET AL. | |
|---|---|---|---|
| | Examiner Lakshmi S. Channavajjala | Art Unit 1615 | |

***-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--***

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to *4-13-06; 6-23-06*.

2. ☒ The allowed claim(s) is/are *1-7, 9-12,14-35 and 47*.

3. ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
   a) ☒ All b) ☐ Some* c) ☐ None of the:
      1. ☒ Certified copies of the priority documents have been received.
      2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
      3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
**THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.**

4. ☐ A SUBSTITUTE OATH OR DECLARATION must be submitted. Note the attached EXAMINER'S AMENDMENT or NOTICE OF INFORMAL PATENT APPLICATION (PTO-152) which gives reason(s) why the oath or declaration is deficient.

5. ☐ CORRECTED DRAWINGS ( as "replacement sheets") must be submitted.
   (a) ☐ including changes required by the Notice of Draftsperson's Patent Drawing Review ( PTO-948) attached
      1) ☐ hereto or 2) ☐ to Paper No./Mail Date _____.
   (b) ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____.

**Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).**

6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

The drawings submitted on 4-17-02 have been accepted.

**Attachment(s)**

1. ☒ Notice of References Cited (PTO-892)
2. ☐ Notice of Draftperson's Patent Drawing Review (PTO-948)
3. ☐ Information Disclosure Statements (PTO-1449 or PTO/SB/08), Paper No./Mail Date _____
4. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
5. ☐ Notice of Informal Patent Application (PTO-152)
6. ☒ Interview Summary (PTO-413), Paper No./Mail Date 6-27-06
7. ☒ Examiner's Amendment/Comment
8. ☒ Examiner's Statement of Reasons for Allowance
9. ☐ Other _____.

Lakshmi

LAKSHMI CHANNAVAJJALA
PRIMARY EXAMINER
AU 1615

**EXAMINER'S AMENDMENT**

An examiner's amendment to the record appears below. Should the changes and/or additions be unacceptable to applicant, an amendment may be filed as provided by 37 CFR 1.312. To ensure consideration of such an amendment, it MUST be submitted no later than the payment of the issue fee.

Authorization for this examiner's amendment was given in a telephone interview with Brian O'Shaughnessy on 6-23-06.

The application has been amended as follows:

Specification:

On page 1, below the title insert "this application is a 371 of PCT/FR00/01971 filed on 07/07/2000."

On page 5, lines 7-8 replace the words "Dimethicone and Simethicone" with "DIMETHICONE and SIMETHICONE" respectively.

On page 6, after line 17, insert the heading "Brief description of Drawings"

Claims:

In claim 1, line 2 delete the word "disposed"

In claim 21, line 2 delete the word "disposed"

In claim 2, line 2 insert "(HPMC)" after the word hydroxypropylmethylcellulose

The following is an examiner's statement of reasons for allowance:

Instant claims are drawn to a pharmaceutical composition in the form of granules, wherein each granule comprises a neutral microgranule on which is a composition comprising micronized fenofibrate, surfactant and a cellulose binder. Instant independent claims require specific percentages of micronized fenofibrate and cellulose binder or their ratios. Prior art of record teaches compositions containing high percentages of micronized fenofibrate in combination with polyvinylpyrrolidone (PVP) and cross-linked PVP as a binder. Where cellulose binder and surfactant are employed in combination with micronized fenofibrate, the prior art of record does not teach the claimed percentages (or ratios) of fenofibrate and the binder. Applicants compared the bioavailability of the fenofibrate formulations (containing claimed percentages of fenofibrate and cellulose binder) with that of the prior art fenofibrate compositions-tablets as well as capsules (containing lower fenofibrate and higher cellulose binder) and showed that the instant compostions achieve higher bioavailability even at a lower dose of fenofibrate than the prior art formulations.

Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lakshmi S. Channavajjala whose telephone number is 571-272-0591. The examiner can normally be reached on 9.00 AM -6.30 PM

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward can be reached on 571-272-8373. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Lakshmi S Channavajjala
Primary Examiner
Art Unit 1615
July 6, 2006

# EXHIBIT 30

**WHAT IS CLAIMED IS:**

1. A pharmaceutical composition comprising micronized fenofibrate, a surfactant and a binding cellulose derivative as a solubilization adjuvant, wherein said composition contains an amount of fenofibrate greater than or equal to 60% by weight.

2. The composition as claimed in claim 1, wherein the binding cellulose derivative, which is a solubilization adjuvant, is hydroxypropylmethylcellulose.

3. The composition as claimed in claim 2, wherein the hydroxypropylmethylcellulose has an apparent viscosity of between about 2.4 and 18 cP.

4. The composition as claimed in claim 3, wherein the hydroxypropylmethylcellulose has an apparent viscosity of between about 2.4 and 3.6 cP.

5. The composition as claimed in claim 1, wherein said composition contains an amount of fenofibrate greater than or equal to 70% by weight relative to the weight of the composition.

6. The composition as claimed in claim 5, wherein said composition contains an amount of fenofibrate greater than or equal to 75% by weight relative to the weight of the composition.

7. The composition as claimed in claim 1, wherein the surfactant is selected from the group consisting of polyoxyethylene 20 sorbitan monooleate, Montane® 20, sucrose stearate and sodium lauryl sulfate.

8. The composition as claimed in claim 1, wherein the surfactant represents between about 1 and 10% by weight relative to the weight of the fenofibrate.

9. The composition as claimed in claim 8, wherein the surfactant represents between 3 and 5% by weight relative to the weight of the fenofibrate.

10. The composition as claimed in claim 2, further comprising a fenofibrate/HPMC mass ratio between 5/1 and 15/1.

11. The composition as claimed in claim 1, wherein the binding cellulose derivative represents between about 2 and 15% by weight of the composition.

12. The composition as claimed in claim 11, wherein the binding cellulose derivative represents between about 5 and 12% by weight of the composition.

13. The composition as claimed in claim1, wherein said composition further contains at least one excipient.

14. The composition as claimed in claim 13, wherein the excipient is a diluent.

15. The composition as claimed in claim 14, wherein the diluent is lactose.

16. The composition as claimed in claim 13, wherein the excipient is an antifoaming agent.

17. The composition as claimed in claim 16, wherein the antifoaming agent is α-(trimethylsilyl)-γ-methylpoly[oxy(dimethylsilylene)] or a mixture of α-(trimethylsilyl)-γ-methylpoly[oxy(dimethylsilylene)] with silicon dioxide.

18. The composition as claimed in claim 13, wherein the excipient is a lubricant.

19. The composition as claimed in claim 18, wherein the lubricant is talc or colloidal silicon dioxide.

20. The composition as claimed in claim 1, wherein the mean size of the fenofibrate particles is less than 15 μm.

21. The composition as claimed in claim 20, wherein the mean size of the fenofibrate particles is less than 8 μm.

22. The composition as claimed in claim 1, wherein said composition is in the form of granules comprising:

(a) a neutral core; and

(b) an active layer, which surrounds the neutral core;

wherein said neutral core may include lactose, mannitol, a mixture of sucrose and starch or any other acceptable sugar, and wherein said active layer comprises the micronized fenofibrate, the surfactant and the binding cellulose derivative.

23. The composition as claimed in claim 1, wherein said composition has a dissolution profile of less than 10% at 5 minutes and more than 80% at 20 minutes according

to the European Pharmacopoeia in a dissolution medium constituted by water with .025 M sodium lauryl sulfate.

24. A method for preparing the composition as claimed in claim 22, wherein said granules are prepared by assembly on the neutral core, by spraying an aqueous suspension containing the surfactant, the solubilized binding cellulose derivative and the micronized fenofibrate in suspension.

25. An immediate release fenofibrate formulation comprising micronized fenofibrate and a binding cellulose derivative wherein said formulation has a dissolution profile of less than 10% at 5 minutes and more than 80% at 20 minutes according to the European Pharmacopoeia in a dissolution medium constituted by water with .025 M sodium lauryl sulfate.

26. The immediate release formulation according to claim 25, wherein said formulation has a dissolution profile of less than about 5% at 5 minutes and more than about 90% at 20 minutes.

27. An immediate release fenofibrate composition comprising:

(a) a neutral core;

(b) an active layer, which surrounds the core; and

(c) an outer layer;

wherein said active layer comprises micronized fenofibrate, a surfactant and a binding cellulose derivative; and wherein said formulation has a dissolution profile of less than 10%

at 5 minutes and more than 80% at 20 minutes according to the European Pharmacopoeia in a dissolution medium constituted by water with .025 M sodium lauryl sulfate.

28. The immediate release formulation of claim 27, wherein said formulation comprises less than 20% by weight of the neutral core; more than 60% by weight of the micronized fenofibrate; less than 20% by weight of binding cellulose derivative and more than 3% by weight of the surfactant.

29. The composition as claimed in claim 27, wherein the outer layer comprises a hydrosoluble binder.

30. The composition as claimed in claim 29, wherein the hydrosoluble binder of the outer layer is HPMC.

31. The composition as claimed in claim 30, wherein hydroxypropylmethylcellulose is chosen among hydroxypropylmethylcellulose having an apparent viscosity of 3 cP or 6 cP or 15 cP or a mixture thereof.

32. The composition as claimed in claim 27, wherein the outer layer further comprises talc.

33. The composition as claimed in claim 32, wherein the outer layer comprises a HMPC/talc mass ratio between 1/1 and 5/1.

34. A method of reducing food effect when treating hypertriglyceridemias in a patient in need thereof comprising administering to the patient an effective amount of the composition according to claim 1.

35. A method of reducing food effect when treating hypercholesterolemias in a patient in need thereof comprising administering to the patient an effective amount of the composition according to claim 1.

36. A method of reducing food effect when treating hyperlipidemias in a patient in need thereof comprising administering to the patient an effective amount of the composition according to claim 1.

37. The method according to claim 34, wherein said patient is fed a high fat containing meal and the bioavailability of fenofibrate in said patient is equivalent to said patient when fasted.

38. The method according to claim 34, wherein said patient is fed a at least 800-1000 calories 50% of which are from fat and the bioavailability of fenofibrate in said patient is equivalent to said patient when fasted.

39. The method according to claim 34, wherein said patient is fed a therapeutic lifestyle change diet and the bioavailability of fenofibrate in said patient is equivalent to said patient when fasted.

40. The method according to claim 35 wherein said patient is fed a high fat containing meal and the bioavailability of fenofibrate in said patient is equivalent to said patient when fasted.

41. The method according to claim 35, wherein said patient is fed a at least 800-1000 calories 50% of which are from fat and the bioavailability of fenofibrate in said patient is equivalent to said patient when fasted.

42. The method according to claim 35, wherein said patient is fed a therapeutic lifestyle change diet and the bioavailability of fenofibrate in said patient is equivalent to said patient when fasted.

43. The method according to claim 36, wherein said patient is fed a high fat containing meal and the bioavailability of fenofibrate in said patient is equivalent to said patient when fasted.

44. The method according to claim 36, wherein said patient is fed a at least 800-1000 calories 50% of which are from fat and the bioavailability of fenofibrate in said patient is equivalent to said patient when fasted.

45. The method according to claim 36, wherein said patient is fed a therapeutic lifestyle change diet and the bioavailability of fenofibrate in said patient is equivalent to said patient when fasted.

## ABSTRACT

Pharmaceutical compositions comprising micronized fenofibrate, a surfactant and a binding cellulose derivative as a solubilization adjuvant, wherein said compositions contain an amount of fenofibrate greater than or equal to 60% by weight and methods of producing fenofibrate compositions.